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Congenital Alopecia and Nail Dystrophy Associated With Severe Functional T-Cell Immunodeficiency in Two Sibs

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We report on two sisters affected by congenital alopecia, nail dystrophy, and a severe T-cell immunodeficiency, presumably inherited as an autosomal-recessive disorder. The T-cell defect was characterized by severe functional impairment, as shown by the lack of proliferative response and upregulation of activation markers following mitogen stimulation. The functional abnormality occurred in spite of the presence of phenotypically mature T cells, thus suggesting the qualitative nature of the defect. This is the first observation reported on an ectodermal disorder, characterized by alopecia and nail dystrophy, observed at birth, in association with a primary immunodeficiency. The hypothesis that these two events may be causally related is discussed.

KEY WORDS: alopecia, nail dystrophy, immunodeficiency

INTRODUCTION

T-cell immunodeficiency is present either as a mild defect in a few rare and well-defined syndromes, or as a severe T-cell disorder in combined immunodeficiency (SCID) [Matsumoto et al., 1992; Stiehm, 1993]. SCID is a rare genetic condition transmitted in most cases as an X-linked trait [Cooper and Butler, 1989; Conley, 1992]. Autosomal-recessive forms of SCID, frequently in association with either adenosine deaminase (ADA) or purine nucleoside phosphorylase (PNP) deficiency, have also been described [Cooper and Butler, 1989], thus indicating that multiple mechanisms may underlie the different forms of the disease. Lymphopenia and a profound impairment of both humoral and cell-mediated immunity, presumably related to a stem-cell defect, ultimately result in a nonspecific clinical pattern, characterized by failure to thrive, intractable diarrhea, and life-threatening infections [Gelfand and Dosch, 1983; Cooper and Butler, 1989]. Recently, a few cases with a SCID phenotype, despite a normal or low-normal number of B and T cells, have been described, suggesting that the immunodeficiency may be qualitative in nature [Chatila et al., 1990; Arnaiz-Villena et al., 1992]. We report on 2 sisters affected by congenital alopecia and nail dystrophy associated with a SCID phenotype.

CLINICAL REPORT

A.D. and G.D. were sisters born at term to nonconsanguineous parents following uncomplicated gestations. At birth, both presented with alopecia of the scalp, eyebrows, and eyelashes, nail dystrophy (ridging and pitting of all nails), and bilateral epicanthal folds (Fig. 1).

At age 2 months, A.D. presented with erythrodermia, persistent diarrhea, and failure to thrive. At 6 months, lymph node enlargement and hepatosplenomegaly were noted. Laboratory investigation showed hypereosinophilia and prominent abnormalities of T-cell functions, leading to a diagnosis of immunodeficiency with hypereosinophilia (Omenn syndrome). Despite the severe impairment of T cells, B-cell functions were preserved, as demonstrated by the presence of allohemagglutinins, even though no specific antibodies against T-cell-dependent antigens were found. At age 12 months, following recurrent infections, the patient showed severe failure to thrive and died of bronchopneumonia resistant to therapy.

G.D., born 3 years later, was first evaluated at age 1 month for possible immunological abnormalities. Her weight was 4,350 g (10–25th centile), length 57 cm (50th centile), and head circumference 37.7 cm (50th centile). At age 2 months, she had mild erythrodermia, subsequently complicated by a pyogenic infection. No oral mucosa leucoplakia was found. Immunological in-

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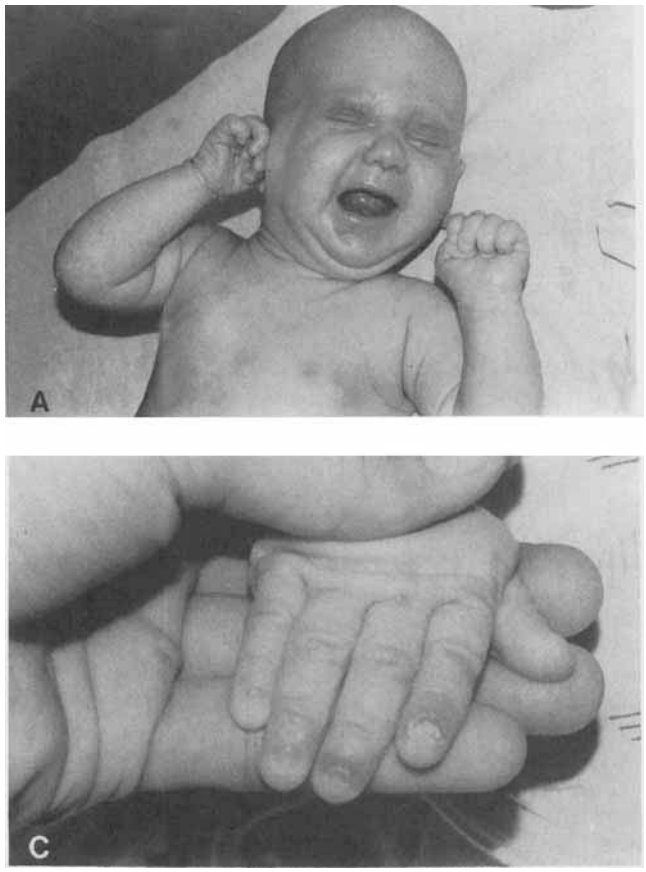

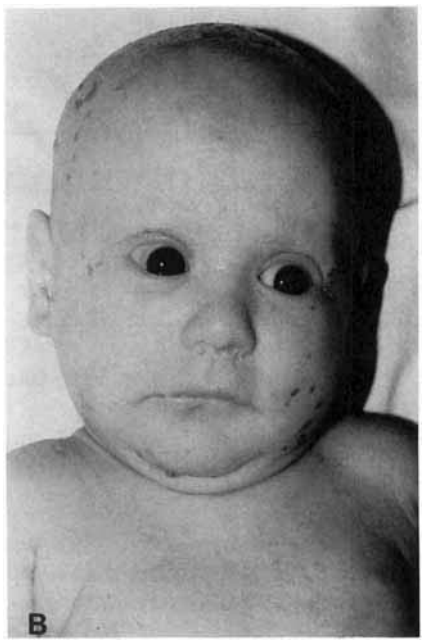

Fig. 1. Views of patients. Alopecia of scalp, eyebrows, and eyelashes in A.D. **(A)** and G.D. **(B). C:** Nail dystrophy in A.D. Nail dystrophy was also present in G.D.

vestigation showed major abnormalities of humoral and cell-mediated immunity, and the patient had continued severe respiratory infections. At 5 months, the child successfully underwent allogeneic human leukocyte antigen (HLA)-matched bone marrow transplantation. It is noteworthy that alopecia and nail dystrophy are still present 1 year following the transplantation.

Results of high-resolution chromosome analysis were normal.

IMMUNOLOGIC STUDIES

The data on lymphocyte surface antigens are summarized in Table I. Expression of most of the membrane markers was similar in both patients. A decrease of mature T lymphocytes (CD3+), accounting for 32% and 25% of total lymphocytes in A.D. and G.D., respectively, was found. The decrease of CD3+ cells was mainly due to a low number of helper T cells (CD4+), ranging between 17–20% during the follow-up period. In contrast, the number of suppressor/cytotoxic population (CD3+CD8+) was normal in both patients. However, since they had a normal, or even high, number of circulating lymphocytes (6.27 and 2.60 $\times$ 10^9/l, respectively), the absolute number of CD3+CD4+ cells was close to the low normal limit in A.D. (1.44 $\times$ 10^9/l), and low, but appreciable, in G.D. (0.52 $\times$ 10^9/l). No circulating immature T cells (CD1+) were found. In both subjects, mature B lymphocytes (CD20+) predominated (63% and 37%, respectively) as a consequence of partial T-cell depletion. Lymphocytes with NK-cell phenotype (CD3−CD56+) were increased, accounting for 23% and 25% of peripheral blood mononuclear cells (PBMC) in A.D. and G.D., respectively, as usually seen in patients with T-cell immunodeficiency. In spite of the presence of circulating mature-type T cells, the proliferative response of PBMC following mitogen stimulation and CD3 crosslinking (CD3 X-L), which mimicks antigen triggering of T-cell receptors (TCR), was absent, as indicated in Table II. The same results were obtained matching the absolute number of CD3+ cells in patients and controls. In contrast to what was observed following T-cell stimulation via TCR/CD3, phorbol myristate acetate (PMA) and ionomycin stimulation induced a normal proliferative response in G.D. Further-

TABLE I. Phenotypic Analysis of Peripheral Blood Mononuclear Cells From the 2 Patients

Surface antigen	Percentage of positive cells		
	Patient A.D.	Patient G.D.	Normal values#
CD1	0.5	0.3	<1
CD3	22	25	50–80
CD4	17	20	45–60
CD5	19	17	50–80
CD8	7	11	10–25
CD11a	97	94	>90
CD11b	98		>90
CD11c	99		>90
CD20	63	37	7–17
CD56	23	25	3–7

TABLE II. Lymphoproliferative Response and Activation Markers Following Mitogen Stimulation or CD3 Crosslinking of Peripheral Blood Mononuclear Cells

	3H-thymidine incorporation (counts/min)			
	Patient A.D.	Control	Patient G.D.	Control
None	440	1,100	300	1,136
PHA	2,237	39,062	1,416	78,379
ConA	1,254	35,716	213	83,286
PwM	787	27,418	257	36,528
CD3 X-L	286	12,543	170	32,760

	Percentage of positive cells			
	Patient A.D.	Control	Patient G.D.	Control
CD3+CD25+	1.9	21.2	5.0	29.2
CD3+DR+	0.2	14.5	2.5	27.8
CD3+CD71+	4.0	21.5	5.1	28.9

more, in vitro stimulation with phytohemagglutinin (PHA) failed to induce the activation markers on T lymphocytes, such as HLA-DR antigens, IL-2 receptor α chain (CD25), and transferrin receptor (CD71) (Table II). The presence of maternal engraftment was excluded by analysis of highly polymorphic DNA regions.

Overall, both patients had a severe immunodeficiency, qualitative in nature and characterized by a predominant involvement of T-cell functions, despite the presence of phenotypically mature T cells.

DISCUSSION

Here we report on 2 sisters affected by alopecia of the scalp, eyebrows, and eyelashes, and nail dystrophy, associated with a primary severe immunodeficiency, presumably inherited as an autosomal-recessive disorder. Alopecia and nail dystrophy are also found in other syndromes. Among these, dyskeratosis congenita (DC) is inherited as an X-linked disorder [Conner et al., 1986; Arngrimsson et al., 1993], although genetic heterogeneity has been suggested [Tchou and Kohn, 1982; Pai et al., 1989]. Diagnostic criteria include the classical triad, consisting of a reticular pattern of hyper- and hypopigmentation of the skin, nail dystrophy, and mucosal leucoplakia [Davidson and Connor, 1988]. This genetic disorder is often associated with bone marrow failure [Gutman et al., 1978; Friedland et al., 1985]. Mild T-cell abnormalities, in association with an apparently normal lymphocyte-activation process, have also been described in patients with this syndrome [Lee et al., 1992]. However, in our patients two of the major diagnostic criteria of DC, i.e., abnormal pigmentation of the skin and mucosal leucoplakia, were lacking, and furthermore, the immunological abnormalities were different from those reported in patients with DC in both severity of clinical course and type of alterations [Ortega et al., 1972; Lee et al., 1992].

Increasing evidence indicates that the SCID phenotype is a heterogeneous condition [Matsumoto et al., 1992], in which a block at different stages of cell differentiation may occur [Cooper and Butler, 1989]. In most cases, both T and B lymphocytes are involved in the process. In a few cases, the involvement of B cells is indirect, due to the lack of T-cell help. Point mutations of the gene located on chromosome Xq13 and encoding for the γ chain of the IL-2 receptor have recently been described in the X-linked form of SCID [Leonard et al., 1985; Noguchi et al., 1993]. In the autosomal-recessive forms, a deficiency of ADA or PNP has been found only in a few cases, but the pathogenesis of most cases remains unknown [Cooper and Butler, 1989]. In the sibs described here, T-cell deficiency seems to be, at least in part, qualitative in nature, in that circulating mature T cells were present, but failed to undergo mitogen-induced activation and cell-cycle progression. Recently, a few patients with such a qualitative disorder, i.e., activation defects, have been described [Chatila et al., 1990; Arnaiz-Villena et al., 1992; Gelfand, 1993]. The activation process is initiated by the interaction of membrane receptors with the ligand; a number of intracytoplasmic molecules and nuclear transcription factors participate in the activation process by propagating signals from external membrane to nuclei [Ashwell and Klausner, 1990; Klausner and Samelson, 1991; Beyers et al., 1992]. This cascade of events ultimately results in transcription of multiple genes and cell activation. Virtually, all the steps involved in this process may be affected and induce immunodeficiency [Gelfand, 1993]. In the second sib, a normal proliferative response following PMA and ionomycin stimulation was observed. Since PMA directly activates protein kinase C, bypassing early tyrosine phosphorylation events following TCR/CD3 triggering, this observation would suggest a block in the transmission of signals in our patients located upstream to protein kinase C.

Whether there is a causal relationship between alopecia, nail dystrophy, and immunodeficiency in our patients is an intriguing question. Alopecia has been found sporadically in patients with Omenn syndrome and interpreted as a consequence of the severe skin involvement [de Saint-Basile et al., 1991]. It should be noted that in both our patients alopecia was observed at birth, before the patients developed erythrodermia. In addition, in Omenn syndrome alopecia disappears following bone marrow transplantation, thus supporting its classification as an acquired disorder. In our second sib, alopecia persisted 1 year following successful bone marrow transplantation. This finding suggests that the alopecia in our patients is primitive in nature. To support the hypothesis that the association between alopecia and immunodeficiency is not by chance, there is also the experimental evidence that athymic mice completely lack body hair (nude mice). Again, alopecia has also been found in association with T- and/or B-cell immunodeficiency in short-limb dwarfism, a rare immunodeficiency syndrome [Hong, 1989]. Taken together, these observations suggest a relationship between alopecia and the immunodeficiency described in the 2 sisters, possibly related to a common gene defect. Molecular investigation is needed to find out which gene alterations are involved in determining lymphocyte activation defect and alopecia.

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